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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/616,371 03/15/96 STAMLER J DUK96-03PA

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EXAMINER

CELSA, B

ART UNIT

PAPER NUMBER

1627

DATE MAILED:

06/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

file copy

Office Action Summary	Application No. 08/616,371	Applicant(s) Stamler
	Examiner Bennett Celsa	Group Art Unit 1627

☒ Responsive to communication(s) filed on Mar 2, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 4, 5, 9, 10, 12, 13, and 15-34 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) 4, 9, 12, 16-30, 33, and 34 is/are allowed.

☒ Claim(s) 5, 10, 13, 15, 31, and 32 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Response to Amendment

Applicant's amendment dated 3/2/00 in paper no. 28 is hereby acknowledged.

Claims 4-5, 9-10, 12-13 and 15-34 are currently pending and under consideration..

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objection(s) and/or Rejection(s)

The 102/103 anticipation rejection over the Stamler WO 93/09806 (5/93) reference and the Stamler reference further in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier), Klatz et al., U.S. Pat. No. 5,395,314 (3/95: file 6/93 or earlier) and Hunter, U.S. Pat. No. 5,152,979 (10/92). are hereby withdrawn to the extent that the claims are directed to S-nitrosylated Hb (w/o heme Fe oxidation) and the use thereof in the light of the submitted Stamler Declaration and the following reasons.

Regarding the Stamler document as interpreted by the Examiner in view of the Stamler Declaration evidence it appears to the Examiner that the Stamler example when taken separately and in view of the entire document teaching of S-nitrosylation of different proteins, including hemoglobin would suggest reacting SNOAc (e.g. S-nitroso-N acetylcysteine) with hemoglobin in equimolar amounts at pH 6.9. However, after careful reevaluation of the Stamler Declaration evidence and especially the reproduction of the above reference experimental conditions and the inability to produce S-nitrosylation without detectable heme Fe oxidation, the Examiner believes that the above reference conditions which lack the "critical" requisite pH range (e.g. 7.4-9.2) as

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disclosed and presently claimed (e.g. claims 33-34) is nonenabled for producing S-nitrosylated hemoglobin.

New Objection(s) and/or Rejection (s)

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER REJECTION)..

To the extent that the new composition claims fail to include the phrase “S-nitrosylation without detectable oxidation of the heme Fe” the newly added claims are necessarily broader than original claims 9 and 12. Pages 11 and 12 pointed to for support for the new claims clearly indicates that the reference methods result in protein S-nitrosylation “at one or more thiol groups without modifying the metal” (see specification at page 11, lines 20-30; see also specification page 3, lines 1-5 : “ ... in a procedure which avoids oxidation of the heme”).

4. Claims 10 and 13 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling.

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Critical or essential method parameters: which include reagent concentration, pH and presence and concentration of buffer, necessary to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

For instance the specification specifically states on page 77, lines 25-30 that "... the balance between oxidation and nitrosothiol formation is dependent upon the ratio of nitric oxide to hemoglobin and the buffer environment. Accordingly, NO: heme concentrations are critical to practicing the presently claimed methods and the achieving of the presently claimed compositions.

Finally, the submitted Stamler Declaration provides further evidence that the choice of nitrosating agent, the amount of agent vis a vis hemoglobin concentration, and pH are critical toward obtaining stable S-nitrosylation of hemoglobin.

5. Claim 15 is rejected under 35 U.S.C. 103(a) as obvious over Stamler et al, WO 93/09806 (5/93).

Claim 15 is directed to a method for regulating delivery of oxygen and NO in various redox forms by administering a mixture of a low molecular weight thiol or nitrosothiol and hemoglobin.

Stamler et al. teach that nitrosylated low molecular weight thiols (e.g. N-acetyl cysteine) serve as NO donating compounds (e.g. delivery of NO) which are therapeutically useful as smooth muscle relaxants, vasodilators and platelet inhibition (e.g. see abstract and pages 1-2 of Stamler).

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Similarly to low molecular weight thiols, the Stamler reference further teaches that proteins (including hemoglobin), which are nitrosylated on oxygen, carbon or nitrogen sites possess the same therapeutic utility as nitrosylated/nitrated low molecular weight thiol compounds. (E.g. see page 6, lines 13-15; page 7, lines 17-21; and claims).

The Stamler reference specifically discloses the use of nitrosylated proteins and low molecular weight nitrosating agents (e.g. see pages 1-2; page 24, lines 10-16) preparations thereof for the treatment of disorders by increasing oxygen capacity and transport; modulating CO and NO to tissues; scavenging radicals and vasodilation such as treating lung diseases (e.g. ARDS) and hypoxic disorders (E.g. see pages 19-25 and claims).

Further it is known in the art that hemoglobin is involved in regulating oxygen metabolism by its ability to bind reversibly to blood oxygen and thus facilitate the capability of blood to transport oxygen to bodily tissues (e.g. see bottom of page 19-top of page 20).

Accordingly, it would have been obvious to combine a low molecular weight thiol or nitrosothiol with hemoglobin to deliver oxygen or NO since the Stamler reference teaches the use of the same compounds separately to effectuate the same function.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Stamler et al. in view of Feola et al., U. S. Pat. No. 5,439,882 (8/95: filed 5/93 or earlier) and Hunter, U.S. Pat. No. 5,152,979 (10/92).

Claim 5 is directed to a malaria treatment using red blood cells comprising S-nitrosothiols

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The Stamler et al. reference discloses the use of S-nitrosating agents (e.g. low molecular weight e.g. glutathione and hemoglobin derivatives) to treat disorders by achieving a variety of physiological effects including vasodilation; radical scavenging ; NO and oxygen delivery.

Stamler does not disclose the use of nitrosating agent(s) to treat malaria.

Feola et al. disclose the use of “blood substitutes” to restore blood volume, transport oxygen and reduce vasoconstriction (e.g. vasodilate) by the use of hemoglobin alone or combined with glutathione as a blood substitute to treat blood disorders (e.g. sickle cell anemia) (e.g. see Abstract, examples and columns 1 and 7).

Hunter discloses that malaria is a blood disorder which results in ischemia caused by compromised microvasculature (e.g. see abstract and col. 1).

The Stamler et al. reference provides the skilled artisan with motivation to use nitrosating agents alone (e.g. nitrosothiols) or combined to treat disorders of diseases to which vasodilation and oxygen/NO transport would prove to be therapeutic.

It would have been obvious to the skilled artisan at the time of applicant's invention to utilize thionitrosating agents (e.g. nitrosothiols) as blood substitutes to treat malaria since the Feola reference discloses the use of hemoglobin and thiol containing blood substitutes to treat anoxic blood disorders e.g. malaria as disclosed by Hunter; and Stamler provides a reasonable expectation that nitrosating agents will be successful to achieve the desired effects of blood substitutes.

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7. Claims 31 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by or alternatively under 35 USC 103 as being obvious over Chem. Res Tox. 1990 Vol. 3, pages 289-291.

The reference discloses a method of transferring the nitrosyl group to sulfur (as well as oxygen, nitrogen and sulfur) of heme proteins, including hemoglobin to thus form SNO-hemoglobin by reacting hemoglobin in pH 7.4, 0.01 buffer (see table 1) under anaerobic conditions in excess nitric oxide (e.g. @ $2 \times 10^{-3} \text{M}$) (e.g. see page 289 under "Results and Discussion"). The reference NO and hemoglobin concentrations are within the scope of the presently claimed invention.

It is noted that a "composition" comprising an S-nitrosylated hemoglobin in which additionally other moieties (e.g. carbon, oxygen and nitrogen) are within the scope of the present composition claims.

The isolation of the nitrosated hemoglobin species and/or the spectrophotometric determination (e.g. page 290) presumably in air would be expected to form the the oxyhemoglobin species. Alternatively, it would have been obvious to one of ordinary skill in the art to generate the oxygenated hemoglobin species by air oxidation especially since the reference specifically points to a nitrosation process which occurs under aerobic conditions. E.g see page 290, left column and footnote 4. The degree of heme oxidation (e.g. "nondetectable") of the reference nitrosylated hemoglobin would be met inherently by the reference which utilizes a

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method within the scope of the presently claimed invention. The Examiner lacks the facilities to do testing.

Double Patenting

8. Claims 4-5, 9-10,12-13 and 15-34 of this application conflict with claims which are present in Application No.08/667,003 and 08/796,164. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

9. It is noted that allowable subject matter has been indicated (see below). Accordingly, at the time of allowance, related applications will be further evaluated for overlapping subject matter which may (or may not) result in the removal or addition of double patenting rejection(s). Applicant's assistance in this regard would be appreciated

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Allowable Subject Matter

10. Claims 4, 9, 12 and 16-30 and 33-34 are allowable over the prior art of record.

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

June 5, 2000

**BENNETT CELSA
PRIMARY EXAMINER**

